PCT/GB 00/03343

INVESTOR IN PEOPLE

GB0003343

10/030573

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

PRIORITY DOCUMENT

SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

REC'D 17 OCT 2000

WIPO PCT

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed R. Mahoney

Dated 02 OCT 2000

Patents Form 1/77

Patents Act 1977
(Rule 16)

The Patent Office

03SEP99 E4[illegible]990-0[illegible]002884
P01/7700 0.00 - 9920732.6

1/77

THE PATENT OFFICE
A
03 SEP 1999
RECEIVED BY POST

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — P24444/PKE/BOU

2. Patent appli[illegible] 9920732.6 — -3 SEP 1999
(The Patent Office will fill in this part)

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Sulzer Vascutek Limited
Newmains Avenue
Inchinnan
Renfrewshire
PA4 9RR

Patents ADP number *(if you know it)* 7187263001

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4. Title of the invention — "Sealant"

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Murgitroyd & Company
373 Scotland Street
GLASGOW
G5 8QA

Patents ADP number *(if you know it)* 1198013

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*
–		

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*
–	

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Yes

SEALANT

The present invention relates to a non-gelatine based coating or sealant for porous vascular prostheses, and to a method of making that coating or sealant.

Porous vascular prostheses constructed from textiles (such as polyester) are normally woven or knitted and ultimately rely on host tissue penetrating into the spaces between the yarns. To function in the long term the prostheses must, therefore, acquire porosity whilst at implant bleeding through the prosthesis wall must be prevented or at least limited to an acceptable level.

In the past this dilemma has been resolved by soaking a porous textile-based prosthesis in the patient's blood which then clots to form a seal. This pre-clotting technique is time consuming, exposes the prosthesis to potential contamination and may be ineffective in patients with reduced clotting ability (either reduced spontaneous blood clotting or through administration of anti-platelet or anti-thrombotic medication).

More recently, vascular prostheses have been pre-sealed

Dextrans of this molecular weight are freely water-soluble. To form a useful graft sealant, the dextrans must be rendered insoluble. However, dextrans are not easily cross-linked as they have limited reactive sites to form intermolecular bonds. The available groups are almost exclusively hydroxyl (OH) groups.

British Patent No 854,715 describes the formation of a dextran-based polymer by using epichlorohydrin. However the epichlorohydrin-based approach forms very stable cross-links so that the resultant polymer is resistant to both enzymatic and hydrolytic attack and does not biodegrade. Epichlorohydrin cross-linked dextran is, therefore, unsuitable as a vascular graft sealant as it is not bioresorbable and would not permit tissue ingrowth within the timescale required. EP-B-0,183,365 and US-A-4,747,848 both describe a gelatin-based sealant in which the time-scale of reabsorption is controllable.

To overcome this problem, a novel dextran-based polymer has been produced which is bioresorbable through hydrolysis in the time scale of interest.

The present invention provides a bioresorbable sealant composition comprising a polymer formed by reaction between dextran, formaldehyde and urea. Whilst the dextran polymer product is insoluble, the polymer is formed with bonds that are sufficiently labile to permit resorption at an appropriate rate for tissue ingrowth. Furthermore, when the cross-linked polymer breaks down, it does so into simple products all of which have a low molecular weight and which are easy for the body to dispose of.

The term "dextran" as used herein includes naturally

between 20 to 250°C for a time sufficient to allow polymerisation to occur.

The formaldehyde is conveniently added in the form of formalin (a 37% aqueous solution of formaldehyde hydrate). Alternatively, it would be possible to bubble formaldehyde gas through the mixture of step (a) to achieve the required reaction. The quantity of formaldehyde required may be determined stochiometrically having regard to the amount of urea added in step (a). We have found that an amount of formaldehyde equivalent to 50 to 100% (by weight) with reference to the amount of urea achieves the required result, with 70 to 80% (by weight) being preferred.

In a further aspect, the present invention provides a method of producing a non-porous graft by impregnating a flexible porous material with a mixture of dextran, urea and formaldehyde, and incubating said impregnated material at temperatures of from 20°C to 250°C for a time sufficient to facilitate cross-linking of said dextran.

Preferably the temperature selected is from 30°C to 200°C, for example is from 45°C to 160°C.

The flexible porous material to be treated by the present invention may be of any conventional type or construction. Particular mention may be made of polyester (e.g. DACRON™) knitted or woven fabric and also of PTFE-based materials. Additionally, expanded PTFE may be coated as described since, although the material itself is non-porous, porosity will be introduced when the graft is stitched into place by the surgeon.

likely to comprise sugar units, urea, formaldehyde and small complexes of the latter components. It is of course possible to modify the hydroxyl groups available on the dextran for reaction (see for example EP-B-0,183,365).

The invention is now further described by reference to the following, non-limiting, examples (together with a comparative example).

Example 1

90 ml of water was added to 50 g of 40,000 molecular weight dextran and manually mixed to encourage the dextran to enter into solution. Afterwards the mixture was placed on a magnetic stirrer and allowed to mix continuously for 15 minutes or until the solution was clear and particle free.

5 g of urea were then added to the solubilised dextran and the mixture placed back on the magnetic stirrer for a further 15 minutes to ensure that the urea had entered into solution with the dextran. Finally, 10 ml of formalin (a 38% (w/v) aqueous solution of formaldehyde hydrate) providing 3.8 g of formaldehyde was added to complete the mixture which was again allowed to stir for 15 minutes. This mixture was the impregnated into knitted polyester grafts using vacuum techniques.

Gels were formed by placing the dextran impregnated grafts in an oven at 150°C for 2 hours. During this time a cross-linking reaction was taking place. Grafts were washed for a minimum of four hours to ensure removal of any residual formaldehyde. Finished grafts were softened by exposure to 100% glycerol for 10

known weight in buffer and weighing the grafts again after drying to measure the amount of sealant remaining. Urea formaldehyde cross-linked dextran was found to be hydrolysed at a rate comparable to the gelatin sealant of EP-B-0,183,365.

The hydrolysis profiles of urea-formaldehyde cross-linked dextran and formaldehyde cross-linked gelatin grafts are detailed in Table 1. Hydrolysis was performed at 37°C over a period of up to 4 weeks at 125 rpm.

Table 1.
Comparative hydrolysis results for dextran and gelatin coated vascular grafts. The gelatin coated grafts were produced in accordance with Example 1 of EP-B-0,183,365.

Day	% gel degraded	
	Dextran	Gelatin*
0	0	0
3	5	30
6	15	70
12	25	95
28	95	100

*Comparative Example

Example 4 - Implantation

Grafts prepared according to Example 1 were implanted into the abdominal aorta of dogs for 2 weeks and 4 weeks respectively. Histological examination of the